Original Article

Comparative evalution of intrathecal 0.5% heavy bupivacaine alone with intrathecal preservative free midazolam(1.5mg) and 0.5% bupivacaine combination in inguinal hernia surgery

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Abstract

Background: Spinal Anaesthesia is a common anaesthetic technique for inguinal hernia surgery. Many adjuvents have been added intrathecally along with local anaesthetic and their effects are evaluated. Midazolam has been evaluated and found that it prolongs the duration of analgesia along with intraoperative sedation. In the present double blind prospective study we compare the study of 0.5% hyperbaric Bupivaccaine intrathecally alone (Group B) with 0.5% hyperbaric Bupivaccaine Midazolam combination intrathecally (Group BM) in patients undergoing elective ingunal hernia surgery. **Methods:** 100 patients of ASA GradeI\II aged 18-55 years were randomly allocated into 2 groups (50 each) Group B received 0.5%Bupivaccaine 2.6ml +0.3ml normal saline intrathecally and Group BM received 0.5% Bupivaccaine 2.6ml +0.3 ml Midazolam preservative free(1.5mg).We observed the onset of sensory anaesthesia (L_1level), peak sensory level, duration of sensory and motor block, two point regression time, intraoperative sedation score time for first dose of Rescue analgesia along with vital parameters Heart Rate, Systolic and Diastolic Blood Pressure, SPO_2, and Respiratory Rate. **Results:** The time for first rescue analgesia was significantly prolonged in Group BM (390 $\pm$ 79.02 minutes) vs in Group B(271.6 $\pm$ 40.76 minutes) P value < 0.0001, highly significant.. Intraoperative sedation score was more in Group BM(2.46 $\pm$ 0.76) as compared to GroupB(2.08 $\pm$ 0.72) and statistically significant. **Conclusion:** Addition of intrathecal Midazolam (1.5 mg preservative free) to Bupivacaine 0.5% (heavy) significantly prolong the duration of effective analgesia which is reflected as the time to request for first rescue analgesia, along with significant sedation score in GroupBM,and No adverse effects occurred in the form of respiratory depression, pruritis, nausea, vomiting, urinary retention and neurological deficit.

Keywords: Hyperbaric Bupivaccaine, Intrathecal Midazolam, Postoprative analgesia.

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INTRODUCTION

Spinal subarachnoid block is one of the most versatile regional anesthesia techniques used in infraumbilical surgeries. Regional anesthesia offers several advantages over general anesthesia – blunt stress response to surgery, decreases intra-operative blood loss, lowers incidences of post-operative thromboembolic events, and provides analgesia in early post-operative period. Subarachnoid block provides adequate analgesia to patients undergoing infraumbilical surgeries. Among the local anesthetics, 0.5% hyperbaric Bupivacaine is the most commonly used drug for spinal anesthesia as it provides effective sensory and motor block for patient wellbeing and surgeons work. The most important disadvantage of single injection subarachnoid block is the limited duration. The ASA "practice guidelines for pain management in the perioperative setting" stresses on multimodal therapy with two or more analgesic agents used in combination for the control and prolongation of perioperative pain.[1] Therefore in order to minimize and prolong analgesia, a

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number of agents have been added to spinal anesthesia.. Various intrathecal adjuvants such as Opioids, Ketamine, Clonidine and Neostigmine are often added to enhance the duration of spinal anesthesia. Epidural and spinal Opioids have been used but the associated major side effects like sedation, itching, urinary retention, nausea,vomiting, neurological deficit, respiratory depression and tolerance have limited their widespread use.[2] Other adjuvants like Clonidine, Ketamine have also been tried but none is in regular use because of their adverse effects. In the quest for newer, safer intrathecal adjuvant researchers have found benzodiazepine receptors in spinal cord which lead to segmental block of nociception without any adverse effect on cardiovascular and respiratory system. Midazolam is known to produce antinociception and potentiate the effect of local anesthetic when given intrathecally, without any significant side effects. In vitro autoradiography has shown that there is a high density of benzodiazepine (GABA A) receptors in Lamina II of the dorsal horn in the human spinal cord, suggesting a possible role in pain modulation. It has been further proved that intrathecal preservative free Midazolam reduces GABA mediated neurotransmission in interneurons leading to decrease in the excitability of spinal cord dorsal horn neurons. The discovery of benzodiazepine receptors in the central nervous system (Mohler and Okada, 1977)[3] was soon followed by use of intrathecal administration of water soluble benzodiazepine, Midazolam, for pain relief in animals and human beings (Whitwam *et al* 1982, Niv *et al* 1983)[23] In 1992, Serrao *et al*[6] reported therapeutic benefits of intrathecally administered Midazolam (2mg) in patients of chronic mechanical low back pain and results were comparable with epidural Methylprednisolone (80mg). With this information, we are comparing intrathecal Bupivacaine-Midazolam combination with Bupivacaine alone in order to assess duration of sensory block, motor block, hemodynamic changes and postoperative pain relief in inguinal hernia surgery

AIM AND OBJECTIVES

The present study was undertaken with the following aims and objectives:

1. To compare the various aspect of sensory and motor blockade between the two groups.
2. To compare the perioperative hemodynamic changes
3. To compare the duration of effective analgesia between the two groups
4. To observe the perioperative sedation and anyother adverse effects

MATERIALS AND METHODS

The present "comparative study of 0.5% (heavy) intrathecal bupivacaine alone with 0.5% (heavy) intrathecal bupivacaine midazolam combination in patients undergoing elective inguinal hernia repair" was carried out at government medical college and hospital, Nagpur, from August 2013 to August 2015. Ethical committee approval was obtained. This was a hospital based, prospective, randomized double-blind case control trial. For ensuring blinding, randomly allocated coded syringes of drugs were prepared by an anesthesiologist who will not perform subarachnoid block or record the outcome of intraoperative and postoperative period. The patients and the anesthesiologist performing the study was blinded to the content of the drugs contained in the syringes and were randomly allocated in two groups using sealed envelopes.

Sample size estimation

Sample size estimation was done using power and sample size calculation software (Enmaster version 2.0) and total of 100 patients were studied with 50 patient in control group (group B) and 50 patients in study group (group BM).

Inclusion Criteria

- Patients consent
- American Society of Anesthesiologists (ASA) physical status I or II,
- Either gender
- Age between 18-55 years
- Patient undergoing elective inguinal hernia repair (open)

Exclusion Criteria

- Gross spinal deformity
- Infection at the site of injection
- Coagulopathy or other bleeding diathesis
- Known sensitivity to the drugs used in the study,
- Increase intracranial pressure
- Patients who are refusing to participate
- Fixed cardiac output.
- Severe hypovolemia

Statistical Analysis

Continuous variables were presented as mean +/- SD. Categorical variables were expressed in actual numberand percentage. Demographic, hemodynamic and spinal blockade parameters were compared between two groups by performing one way analysis of variation. Multiple comparisons were made by Borferroni T test. Categorical variables were compared in two groups by Pearson's Chi square test. $P< 0.05$ was considered as statistically significant. Statistical software STATA version 13.0 was used for data analysis.

OBSERVATIONS AND RESULTS

The present "comparative study of 0.5% (heavy) intrathecal Bupivacaine alone with 0.5% (heavy) intrathecal Bupivacaine Midazolam combination in patients undergoing elective inguinal hernia repair" was carried out at government medical college and hospital, Nagpur, from August 2013 to August 2015. 100 patients, who were undergoing elective inguinal hernia repair under spinal anesthesia, were randomly allocated in two groups of 50 each. Group BM (study group): 2.6 ml of 0.5% (Heavy) Inj. Bupivacaine+ 0.3ml of preservative free Midazolam (1.5mg)Group B (control group): 2.6 ml of 0.5% (Heavy) Inj. Bupivacaine + 0.3ml of Normal saline. Total drug volume: 2.9ml. All the patients belonged to ASA class I and II. All patients had successful spinal anesthesia and none required general anesthesia. No patient in both the groups required intraoperative analgesia and sedation.

Table 1: Showing demographic characteristics

Characteristics	Group BM (study)	Group B (control)	P value
Age (years)			
Mean (SD)	41.48 ± 10.08	43.48 ± 8.55	0.2873, NS
Range	18 – 55	18 - 55	
Height (in cm)			
Mean	164 ± 2.26	163 ± 5.20	0.1494, NS
Range	150 – 175	150 - 175	
Weight (in kg)			
Mean	59.56 ± 5.12	59.34 ± 5.13	0.8304, NS
Range	50 – 70	50 - 70	

NS- not significant

The demographic characteristics like age, height, weight, ASA status were comparative in both the groups. All the patients included in the study were males in both the groups.

Table 2: Preoperative vital parameters

PARAMETER	Group BM (study)	Group B (control)	p-value
Pulse rate	80.42 ± 12.25	80.84 ± 11.42	0.8597,NS
Systolic Blood pressure	125.8 ± 11.42	126.04 ± 11.58	0.9171,NS
Diastolic Blood pressure	78.08 ± 10.78	74.84 ± 10.61	0.1332,NS
Respiratory rate	15.2 ± 2. 19	15.2 ± 2.19	0.6760, NS
Oxygen saturation	99.08 ± 0.5657	99.1 ± 0.6145	0.8659, NS

NS= not significant

Table 3: Showing characteristic of spinal blockade

SR No.	Observations	Group BM (study) (n=50)	Group B (control) (n=50)	P value
1	Onset of analgesia (minutes)	2.82 ± 0.71	2.56 ± 0.74	0.0599, NS
2	Level of sensory block (T4-T10)	6.84 ± 1.41	6.60 ± 1.30	0.0599, NS
3	Time to achieve adequate level (minutes)	9.04 ± 1.19	9.44 ± 1.40	0.1256, NS
4	Two segment regression time(minutes)	103.82 ± 21.3	102.3 ± 12.98	0.6658, NS

N.S= not significant

There was no statistically significant difference between the two groups for the characteristics of sensory spinal blockade.

Table 4: Showing duration of motor block

Observation (Duration of motor block)	Group BM (study)	Group B (control)	P- value
Mean	139.1 ± 7.538	137.5 ± 7.576	0.2924,NS

NS= not significant

The duration of motor block in both the groups was comparable and not significant (P – 0.2924)

Table 5: Intraoperative vital parameters

PARAMETER	Group BM	Group B	p-value
Pulse rate	76.5 ± 10.26	81.4 ± 10.60	0.0209,S
Systolic Blood pressure	113.8 ± 9.88	116.52 ± 9.16	0.1566,NS
Diastolic Blood pressure	71.68 ± 9.60	67.52 ± 7.76	0.1895,NS
Respiratory rate	14.38 ± 2.33	14.7 ± 2.15	0.4788,NS
Oxygen saturation	99.02 ± 0.47	99 ± 0.35	0.8107,NS

S= Significant, NS= not significant

The mean pulse rate in Group BM was 76.5 ± 10.26 whereas that of Group B was 81.4 ± 10.60. It has been observed that change in pulse rate (P - 0.0209) was significant in Group BM as compared to Group B. While changes in other vital parameters like SBP, DBP, Respiratory Rate, Spo_2 in both the groups were comparable and statistically not significant

Table 6: Table showing intraoperative sedation score

Observation (Sedation score)	Group BM (study)	Group B (control)	P – value
Mean	2.46 ± 0.76	2.08 ± 0.72	0.0121,
Range	1-4	1-3	S

S= Significant

Sedation score of Group BM was significantly more than Group B. P value was significant that is 0.0121. In Group BM, mean sedation score was 2.46± 0.76, the sedation score range from 1-4 whereas in Group B, mean sedation score was 2.08±0.72, the sedation score range from 1-3.

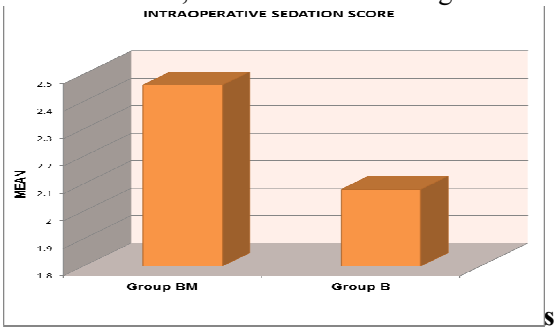

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Table 7: Showing intraoperative complications

Observations	Group BM (study)	Group B (Control)	P - value
Hypotension	1	1	1.0000, NS
bradycardia	0	0	
Shivering	2	2	
Nausea and vomiting	1	1	
Urinary retention	0	0	
Pruritis	0	0	
Neurological deficit	0	0	

N.S= not significant

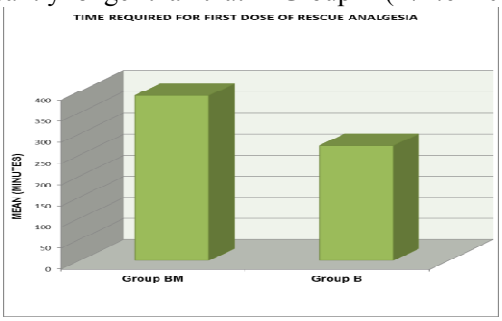
Intraoperative complications were studied in both the group. As shown above, P value was 1.000 which was not significant. Thus there was no significant difference for intraoperative complications between the two groups.

Table 8: Postoperative sedation score

Postoperative sedation score	Group BM (study)	Group B (control)	P – value
Mean	1.42 ± 0.4986	1.48 ± 0.5047	0.5512, NS

NS= not significant

The mean sedation score in Group BM was 1.42 ± 0.4986 and that of Group B was 1.48 ± 0.5047. The observation between two groups was comparable and statistically not significant (P- 0.5512). No postoperative complications were seen in any patients in both the groups. The mean time from onset of the block till the time for first analgesic supplementation was noted in both the groups. Group BM = 390±79.02, Group B = 271.6± 40.76. The P value is less than 0.0001. Thus, this shows that the time to first rescue analgesia in Group BM (390±79.02) was significantly longer than that in Group B (271.6±40.76).



DISCUSSION

Jeremy Bentham said, "Nature has placed mankind under the government of two sovereign masters – pain and pleasure". Relief of pain is professionally rewarding and is a subject that has gained attention in past few years. Epidural and spinal Opioids have been used but the associated major side effects like sedation, itching, urinary retention, nausea, vomiting, respiratory depression and tolerance have limited their widespread use.[2]other adjuvants like Clonidine, Ketamine have also been tried but none is in regular use because of their adverse effects. After discovery of benzodiazepine receptors in the central nervous system and spinal cord, [3] it was thought that itcould be used epidurally and intrathecally for relief from pain. Intrathecal midazolam seems to be promising drug because of absence of aforementioned side effects. Midazolam has shown to have antinociceptive properties. Goodchild CS and Noble J(1987)[13] conducted a pilot study where they demonstrated analgesia and sensory block lasting for as long as 72 hours in the postoperative period.Serro M Juliet et al (1992)[6]compared its effect with epidural steroid for chronic mechanical low back pain. Kim MH et al (2001)[29] studied the clinical efficacy of intrathecal Midazolam for postoperative period and Mi Ja Yun etal (2007)[31]conducted study to evaluate the analgesic effect and sedative effect of intrathecal Midazolam. Further, Shirish chavan et al (2010)[35] conducted study to compare the mean period of analgesia for intrathecal Midazolam 0.5 ml plus Bupivacaine and Bupivacaine alone and to monitor the side effects of intrathecal Midazolam (0.5 ml) plus Bupivacaine and Bupivacaine alone. Dr S Anal kumar et al (2015) conducted this study to compare the subarachnoid block characteristics with Midazolam to intrathecal Bupivacaine. The present study was carried out to evaluate the various aspect of sensory and motor blockade, the perioperative hemodynamic changes, the duration of effective analgesia and the perioperative sedation and any other adverse effects of 1.5 mg Midazolam when given with 0.5% Bupivacaine by intrathecal route in patients going for elective inguinal hernia (open) surgery. The study included 100 patients, with ASA grade I and II. Patients were divided randomly into two groups of 50 each. Group BM (n=50): 2.6 ml of 0.5% (Heavy) Inj. Bupivacaine + 0.3ml of preservative free Midazolam (1.5mg) Group B (n=50): 2.6 ml of 0.5% (Heavy) Inj. Bupivacaine + 0.3ml of Normal saline. Total volume of the drug was 2.9ml in each group. The patients in both the groups were comparable with respect to age, height, weight and ASA status. Both the groups were comparable in respect to the duration of surgery. Various previous studies had used the dose of 1-2 mg single shot intrathecal Midazolam. Keeping in mind the safety and clinical efficacy of dose of single shot Midazolam from the previous studies, we decided to use midazolam in dose of 1.5 mg (0.3ml) intrathecal for our study group. In our study, patients were randomly divided into two groups (study and control) and they received the intrathecal injections of drugs as mentioned above. Different parameters were monitored intraoperatively as well as postoperatively till the rescue analgesia is required.

CONCLUSION

We concluded with the following points:

- Addition of intrathecal Midazolam (1.5 mg preservative free) to Bupivacaine 0.5% (heavy) significantly prolong the duration of effective analgesia which is reflected as the time to request for first rescue analgesia.
- Intraoperative sedation score is more in Group BM. which was statistically significant.
- Intraoperative Heart rate is significantly less in Group BM
- No adverse effects occurred in the form of respiratory depression, pruritis, nausea, vomiting, urinary retention and neurological deficit.

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